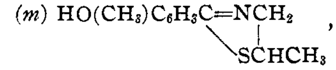
[CONTRIBUTION FROM THE GAYLEY CHEMICAL LABORATORY OF LAFAYETTE COLLEGE AND THE CHEMICAL LABORATORY OF WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

Thiazoline-*m*-cresol. Functional Derivatives and Substitution Products[1]

BY WILLIAM F. HART AND JOSEPH B. NIEDERL

In a previous publication[2] it was reported that of the various thiazolinephenols[3] the 5-methylthiazoline-*m*-cresol,  $\begin{array}{l}(m)\ \mathrm{HO(CH_3)C_6H_3C{=}NCH_2} \\ \qquad\qquad\qquad\qquad \mathrm{SCHCH_3}\end{array}$, which is readily prepared by condensing allyl mustard oil with *m*-cresol, appears to be the most promising in regard to certain physiological properties, such as local anesthetic action. This compound, therefore, was subjected to further studies in the course of which, in addition to the previously reported derivatives,[2] the following new ones were prepared.

Ethers.—In the preparation of the ethers (Table I) the previously published procedure involving the treatment of the sodium salt of the thiazoline-*m*-cresol with the respective alkyl halides or ethyl chloroacetate was followed.[2] The same applies to the preparation of the hydrochlorides and picrates. In the preparation of the nitro derivative the procedure of Babcock and Adams[4] was used and the reduction to the corresponding amine involved the use of stannous chloride essentially as previously described.[2]

Aryloxyacetic Acid.—This acid was prepared from the free base of the ethyl ester of the phenoxyacetic acid by neutralizing a solution of the hydrochloride with sodium bicarbonate and extracting with ether. The ether extracts were dried over anhydrous sodium sulfate and upon evaporation yielded the free base as an oil, which could not be crystallized.

The sodium salt of the phenoxyacetic acid was then prepared by refluxing for one hour a portion of the above ethyl ester with a calculated amount of sodium methylate. Upon cooling the sodium salt separated from the alcoholic solution. The alcoholic solution was evaporated to dryness, and the sodium salt washed with dry acetone.

The hydrochloride of the free phenoxyacetic acid was then prepared by neutralizing a solution of the sodium salt with dilute hydrochloric acid, and evaporating the solution to dryness. The residue was extracted with absolute ethyl alcohol and the filtered alcoholic extract again evaporated to dryness. After washing the residue with dry acetone it was recrystallized once from 95% ethyl alcohol.

Phenylurethan.—The phenylurethan was prepared by heating a portion of thiazoline-*m*-cresol in a sealed test-tube in a boiling water-bath with an excess of phenyl isocyanate. Upon heating for several hours, the contents of the tube solidified when cooled. On further heating, the contents of the tube became a viscous oil which did not change appearance on longer heating. The tube was then opened and the contents dissolved in dry ether. This solution was saturated with dry hydrogen chloride. The voluminous precipitate of the hydrochloride was filtered off and washed with dry acetone until free of color. The free base was prepared by neutralizing a suspension of the hydrochloride in water with sodium bicarbonate and extracting with ether. The ether extracts were dried, evaporated to dryness and the residue taken up in dry benzene. This solution was decolorized with Darco and evaporated to dryness. The compound was secured in crystalline condition by dissolving in a small quantity of acetone and precipitating by the addition of several volumes of petroleum ether.

Sulfonation.—Five grams of thiazoline-*m*-cresol was added to 5 cc. of 15% oleum, and heated in a steam-bath until all had dissolved and a test portion was entirely soluble in cold dilute sodium carbonate solution. The solution was then poured into 30 cc. of cold water and upon stirring, the sulfonic acid crystallized from solution. After cooling, the precipitate was filtered on a sintered glass filter, air dried, washed with small portions of boiling 95% alcohol in which the sulfonic acid is only slightly soluble, and finally with dry acetone. The sulfonic acid is only very slightly soluble in water and in 95% alcohol from which it may be recrystallized by using a large volume of the boiling solvent.

The sodium salt was prepared by adding a calculated amount of sodium bicarbonate to a suspension of the sulfonic acid in water, decolorizing the solution with Darco, and evaporating to dryness. The product was washed with dry acetone. It is very soluble in water, the *p*H of the solution being very near to 7.0. The salt has an alkaline taste which is followed by a sweet taste that is very persistent.

Thiazolinesalicylic Acid and Derivatives.—A solution of four grams of thiazoline-*m*-cresol in 50 cc. of absolute methyl alcohol containing 0.5 g. of sodium was refluxed for fifteen minutes and then transferred to a 125-cc. distilling flask which was packed with glass wool. The flask was set in a metal bath which was kept at a temperature of 80°. The methanol was then distilled off under slight suction with hydrogen bubbling through the solution. After all of the methanol had been distilled over, the temperature within the flask was raised to 170°. The hydrogen was then shut off and carbon dioxide gas was forced through the flask under a slight pressure for three hours. The temperature during this period was maintained at 170–175°.

The methyl and ethyl esters were prepared by dissolving 0.5-g. quantities of the acid in 10–15 cc. of the corresponding absolute methyl or ethyl alcohol. These solutions were then refluxed on a steam-bath with a steady stream

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[1] Parts of this communication were taken from the M.Sc. thesis of Morris Engelman and the M.A. thesis of James H. Turner, the theses to be presented to the faculties of the Graduate School of New York University and of Lafayette College, respectively.

[2] Wm. F. Hart and J. B. Niederl, THIS JOURNAL, **61**, 1145 (1939).

[3] J. B. Niederl, U. S. Patent 2,112,445 (1938); J. B. Niederl, Wm. F. Hart and J. V. Scudi, THIS JOURNAL, **58**, 707 (1936).

[4] Babcock and Adams, *ibid.*, **59**, 2260 (1937).

of dry hydrogen chloride gas passing through for a period of three hours. The excess alcohol was then distilled off, the residue taken up with water to which an excess of saturated sodium carbonate solution was added. This solution was extracted with ether. The ether was washed with small portions of cold water, dried with calcium chloride, filtered, and then saturated with dry hydrogen chloride gas, precipitating the hydrochlorides.

The free esters were prepared from the hydrochlorides by neutralizing an aqueous solution of the hydrochloride with saturated sodium bicarbonate solution. The water insoluble free bases were filtered off, washed with water and recrystallized from 50% aqueous alcohol.

Methiodides.—The free bases were gently refluxed with a slight excess of methyl iodide for two hours. If the methiodides did not crystallize directly in the reaction mixture, the excess methyl iodide was allowed to evaporate spontaneously and the reaction product was taken up in cold dry acetone. The methiodides were crystallized from this acetone solution, and recrystallized once from dry acetone. The methiodides are soluble in water.

TABLE I

No.		Compound	Formula	M. p., °C. (uncor.)	Analyses, % N	
					Calcd.	Found
I		5-Methyl-2-(2′-methyl-4′-hydroxy)-phenylthiazoline	$C_{11}H_{13}OSN$	131	6.76	6.75
	(b)	methiodide	$C_{12}H_{16}OSNI$	166	4.01	4.03
II		Ethers				
	(A)	methyl	$C_{12}H_{15}OSN$	107–108	6.33	6.25
	(Aa)	picrate	$C_{18}H_{18}SN_4$	117	12.44	12.56
	(Ab)	methiodide	$C_{13}H_{18}OSNI$	160	3.85	3.88
	(B)	ethyl, HCl	$C_{13}H_{18}OSNCl$	156	5.15	5.03
	(Ba)	picrate	$C_{19}H_{20}O_8SN_4$	118	12.06	12.15
	(Bb)	methiodide	$C_{14}H_{20}OSNI$	148	3.71	3.68
	(C)	*n*-propyl, HCl	$C_{14}H_{20}OSNCl$	183	4.90	5.30
	(Ca)	picrate	$C_{20}H_{22}O_8SN_4$	121	11.71	11.52
	(Cb)	methiodide	$C_{15}H_{22}OSNI$	101	3.58	3.65
	(D)	isopropyl, HCl	$C_{14}H_{20}OSNCl$	190	4.90	5.00
	(Da)	picrate	$C_{20}H_{22}O_8SN_4$	107	11.71	12.01
	(Db)	methiodide	$C_{15}H_{22}OSNI$	93	3.58	3.67
	(E)	*n*-butyl, HCl	$C_{15}H_{22}OSNCl$	180	4.67	4.72
	(Ea)	picrate	$C_{21}H_{24}O_8SN_4$	111	11.38	11.35
	(Eb)	methiodide	$C_{16}H_{24}OSNI$	108	3.45	3.55
	(F)	allyl, HCl	$C_{14}H_{18}OSNCl$	163	4.93	5.21
	(Fa)	picrate	$C_{20}H_{20}O_8SN_4$	112	11.76	11.81
	(Fb)	methiodide	$C_{15}H_{20}OSNI$	117	3.60	3.73
	(G)	lauryl, HCl	$C_{23}H_{38}OSNCl$	148	3.39	3.29
	(Gb)	methiodide	$C_{24}H_{40}OSNI$	82	2.70	2.63
	(H)	cetyl, HCl	$C_{27}H_{46}OSNCl$	143	2.99	2.68
	(Hb)	methiodide	$C_{28}H_{48}OSNI$	66	2.44	2.32
	(J)	diethyl amino ethyl, HCl	$C_{17}H_{25}OSN_2Cl_2$	189	7.38	7.57
III		Aryloxyacetic acid, HCl	$C_{13}H_{16}O_3SNCl$	230	4.64	4.31
	(A)	Na salt	$C_{13}H_{14}O_3SNNa$		4.87	4.62
	(B)	ethyl ester, HCl	$C_{15}H_{20}O_3SNCl$	184	4.21	4.34
IV		Phenylurethan	$C_{18}H_{18}O_2SN_2$	105	8.58	8.48
	(A)	hydrochloride	$C_{18}H_{19}O_2SN_2Cl$	167	7.72	7.84
V		Nitro deriv.	$C_{11}H_{12}O_3SN_2$	144	11.10	11.60
	(A)	hydrochloride	$C_{11}H_{13}O_3SN_2Cl$	180	9.70	9.80
VI		Amino deriv.	$C_{11}H_{14}OSN_2$	224	12.61	12.60
	(A)	di-hydrochloride	$C_{11}H_{16}OSN_2Cl_2$	250	9.49	9.24
VII		Sulfonic acid	$C_{11}H_{13}O_4S_2N$	300	4.87	4.53
	(A)	Na salt	$C_{11}H_{12}O_4S_2NNa$		4.74	4.34
VIII		Carboxylic acid	$C_{12}H_{13}O_3SN$	218–220	5.58	5.85
	(A)	Hydrochloride	$C_{12}H_{14}O_3SNCl$	225–230	4.87	4.75
	(B)	Na salt	$C_{12}H_{12}O_3SNNa$		5.13	5.21
	(C)	methyl ester	$C_{13}H_{15}O_3SN$	76–77	5.28	4.93
	(Ca)	hydrochloride	$C_{13}H_{16}O_3SNCl$	181–183	4.64	4.73
	(Cb)	methiodide	$C_{14}H_{18}O_3SNI$	172–175	3.43	3.33
	(D)	ethyl ester	$C_{14}H_{17}O_3SN$	77–78	5.02	4.94
	(Da)	hydrochloride	$C_{14}H_{18}O_3SNCl$	173–175	4.44	4.55
	(Db)	methiodide	$C_{15}H_{20}O_3SNI$	161–163	3.33	3.46
	(Dc)	picrate	$C_{20}H_{20}O_{10}SN_4$	142–143	11.02	10.74

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Summary

A number of new functional derivatives as well as substitution products of 5-methyl-thiazoline-*m*-cresol have been described.

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The Redistribution Reaction. X. The Relative Affinity of Mercury and Lead for Methyl and Ethyl Radicals

BY GEORGE CALINGAERT, HAROLD SOROOS AND HYMIN SHAPIRO

A previous paper[1] of this series has described the redistribution reaction for the interchange of alkyl radicals in alkyl compounds of lead and mercury. In this work, it was shown that mixtures of: (1) dimethylmercury and tetraethyllead and (2) diethylmercury and tetramethyllead, each system containing 50% methyl radicals and 50% lead bonds, undergo redistribution and yield the same equilibrium mixture, in which the mercury shows a greater relative affinity than lead for methyl with respect to ethyl radicals. This difference was expressed by a "relative affinity constant."

$$K = \frac{(\text{Me-Hg})(\text{Et-Pb})}{(\text{Et-Hg})(\text{Me-Pb})}$$

In order to show that this relative affinity constant is a true equilibrium constant whose value, at a given temperature, is independent of the relative proportions of methyl and ethyl radicals, and of lead and mercury bonds, we have checked the value of K, previously determined, by effecting redistribution in a lead alkyl–mercury alkyl system containing different relative proportions of methyl and ethyl radicals and of lead and mercury bonds. Thus, in the present study, a mixture of 60 mole per cent. dimethyldiethyllead and 40 mole per cent. dimethylmercury, a system containing 62.5% methyl radicals and 75% lead bonds, with aluminum chloride as the catalyst, underwent redistribution at 80° in five hours to give a random equilibrium mixture for which the value of the relative affinity constant, K, was found to be 3.4. This value of K is in good agreement with the previously determined value of 4.5 ± 0.4, considering the sensitivity of the constant to slight differences or errors in determining the composition of the product.[2]

The results are given in Tables I and II, and the distillation curve for the reaction products is shown in Fig. 1. The data show that: (1) the recovery of each metal was satisfactory, considering the difficulty of preventing small handling losses, resulting during extraction of the catalyst, filtration, and transfer of material; there was no appreciable decomposition. Also, the per cent. methyl in the product equalled that of

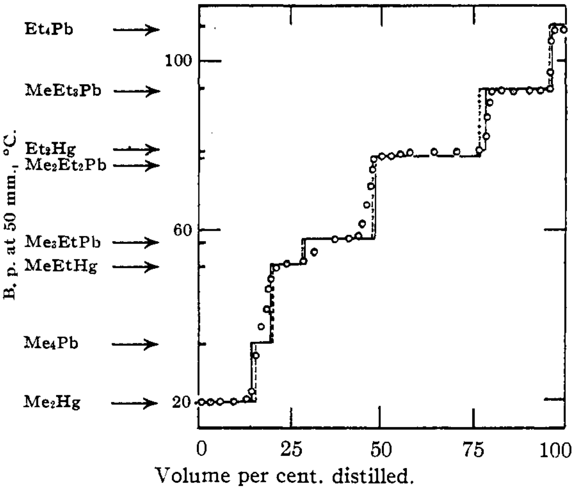

Fig. 1.—Distillation of reaction product from Me_2Hg + Me_2Et_2Pb: solid line calculated for a random equilibrium mixture, with 60% Me radicals, 75% RPb bonds and $K = 3.4$; broken line calculated for the same mixture with $K = 4.55$.

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(1) Calingaert, Soroos and Thomson, THIS JOURNAL, **62**, 1542 (1940).

(2) For an example of this sensitivity, assuming 60% methyl radicals and 75% lead bonds, a variation of per cent. methyl in R_2Hg in the product from 79.4 to 83.0, changes the value of K from (0.197) (0.351)/(0.051)(0.401) = 3.4 to (0.206)(0.360)/(0.042)(0.392) = 4.5, or 32%. The small difference in the composition of the product required to effect this change in the value of K is also shown graphically in Fig. 1.